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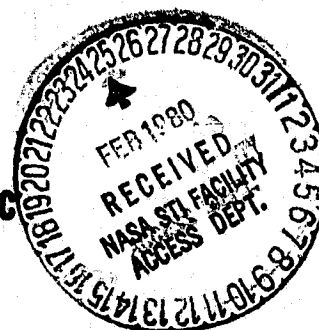
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ABSTRACT

This document presents a final report of the work done under contract NAS9-15487. The original statement of work for this contract contained six major tasks and each of these has been accomplished, but the relations between these tasks were complex and required the transmittal of twenty-four different Technical Information Releases (not including progress reports) to NASA at various times. This work also resulted in nearly a dozen publications or presentations at scientific meetings, and the preparation of a large portion of a seven-year summary of all previous system analysis work. Because of these facts, the present final report will present a unified summary only.

The biomedical monitoring programs of NASA have been designed to support two objectives: (1) the development of a real-time system of data analysis and decision making to assure the greatest possible crew safety and mission success; and (2) the acquisition of information about man's abilities, limitations, and characteristic reactions to weightless space flight. This latter objective is essential to the planning of long duration manned space flight. The most important underlying goal of the Biomedical Systems Analysis Program funded under this contract and its preceding programs (Skylab Medical Data Evaluation Program, NAS9-14523 and Automated System for Integration and Display of Physiological Data, NAS9-12932) was to provide a systems analysis context which integrated the two broad objectives stated above.

It was recognized that the indices normally used to evaluate crew health must be re-evaluated in the light of known physiological adaptive effects in the weightless state. Earlier approaches for maintaining crew health were very comprehensive because of the many uncertainties of space flight. An alternative approach, explored here, was to identify those critical areas where physiological change is most likely to occur, and to develop methods for predicting these trends so that deviations from the norm can be estimated. Consequently, a definition of normal body function during zero-g adaptation was sought by a systematic examination of past flight data coupled with the development of a unified set of physiological

hypotheses. This led to development of the capability to predict a normal zero-g physiological response, based upon simulations using quantitative models. Systems have been designed, using these models, to automatically predict deviation from the normal state by comparing fresh data with past data. Such an approach may offer both clinicians and physiologists a convenient manner in which to describe the real continuum from optimal health to overt pathology.

During the current contractual period, the heaviest emphasis was on interrelating the major biomedical space-flight findings through the formulation of a unified hypothesis for adaptation to space flight. At the same time, analysis techniques were identified that could utilize this information for defining and monitoring inflight physiological status. As in past programs, the contractor continued the support of the experimental activities of principal investigators in several major disciplines. This latter effort involved: (a) developing the predictive capabilities of simulation models in the areas of fluid-electrolyte regulation, erythropoiesis regulation, and calcium regulation; (b) analyzing ground-based and space-flight data; and (c) assisting with the development of objectives, hypotheses, and design of experiments that would help clarify certain critical areas of space-flight adaptation.

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1.0 INTRODUCTION

This report is the final report on contract NAS9-15487 and represents the most recent in a continuing line of systems analysis research in the biosciences at Johnson Space Center.

The first major effort started about 1970 with contract NAS9-11657, Modeling and Integration of Physiological Control Systems. The objective of this initial effort was to provide information needed to make both technical and managerial decisions regarding the development or use of algorithms of the primary homeostatic regulatory mechanisms of man, and the integration of these algorithms into a total interactive simulation system. The following physiological subsystems were identified as being critical for meeting the simulation requirements of the biomedical space-flight research program and for subsequent inclusion in an integrated whole-body model: cardiovascular, respiratory, thermoregulatory, renal, endocrine, and body fluids. Candidate and alternate biological models were identified, selected, implemented, and evaluated for their application to simulating pre-, post-, and inflight physiological testing. This initial study provided a basic framework for evaluating models, defining objectives, and developing software requirements for models and data base management systems.

Progress on contract NAS9-11657 was so encouraging that contract NAS9-12932, Automated System for Integration and Display of Physiological Systems, was initiated to improve the models and to simulate the responses to various biomedical experiments and space environments (such as bicycle ergometry, lower body negative pressure (LBNP), changes in cabin environment, and weightlessness). The major objective of this contract was to develop a whole-body algorithm which would be useful for evaluating hypotheses related to the physiological adaptation to space flight, developing new standards of remote health care for advanced missions, and providing assistance to a real-time monitor during physiological testing. The identification and development of the necessary prototype software systems including

data base systems, parameter identification systems, and automated CRT display systems were secondary benefits of the study. Automated data systems were identified as a required systems analysis capability. The development of a biostatistical analysis system was accomplished as a part of this requirement under contract NAS9-14192, Skylab Endocrine-Metabolic Experiment Data Analysis.

The contract NAS9-14523, Skylab Medical Data Evaluation Program, used the basic elements of the previous contracts to develop a computerized data base as well as an analysis and simulation system. This system consisted of storage elements for Skylab data, statistical software for routine and non-routine data analysis, special purpose data-processing programs, several previously validated simulation models, and the terminals and graphic display units for accessing these elements. The major contract objective was to use this system to process and analyze the data from the major Skylab biomedical experiments, to develop and test individual physiological subsystem hypotheses, and to integrate these hypotheses into a general understanding of physiological adaptation to weightlessness.

These contracts have been directed toward developing the system analysis tools of the biomedical research program and establishing preliminary definitions of health in space. The purposes of the present contract (NAS9-15487) were (1) to use the systems analysis tools to further advance man's understanding of health in space, and (2) to test the effectiveness of the predictive properties that the systems analysis provides. Data analysis and hypothesis development continued under this contract in the fluid and electrolyte, and hematopoietic systems, and was initiated in the musculoskeletal system. In fact, such extensive work was done on the musculoskeletal system that a mathematical simulation model of calcium metabolism was begun and a data base constructed from bed rest calcium studies was developed. The continued hypothesis development and data analysis in these three systems led to the further refinement of the previously developed definitions of health in space. The testing of the predictive qualities of the systems analysis technique had two further purposes:

(1) to explore the use of systems analysis as a management and experimental design tool; and (2) to examine the role of systems analysis in the area of health monitoring.

The use of systems analysis as a research management tool was tested in two ways: (1) as a focal point for all experiments within a given research program; and (2) as an aid for experiment design, development, and evaluation. For example, much of the ground-based research on the erythropoiesis system is performed on rats and mice. Therefore, the erythropoiesis model was modified to relate directly to the mouse. Hypothetically, using related models for the human and the mouse provides a means of predicting human results from mouse experiments. Then, from the predicted model results for the human, human experiments can be designed.

Systems analysis was tested extensively as an aid to experiment design and evaluation in the cardiovascular, fluid/electrolyte, and musculoskeletal systems. Using simulation studies, suggestions can be made concerning the hypotheses that need testing, the relation of these hypotheses to the zero gravity stress, and the direction and magnitude of response of the system to such a stress. From this information, experiment design, including technical requirements and specifications, could be developed. In each investigative area mentioned above, this approach was used to aid NASA investigators in preparing experiment proposals.

Finally, systems analysis was examined for potential application in a health monitoring system. The Shuttle era, potentially, will challenge man's understanding of the physiological changes that occur during exposure to zero gravity. As the Shuttle era advances, the health and physical conditioning of the crewmembers will become less regulated and more diverse than in previous space programs. Thus, upon exposure to zero g, the range and types of physiological changes seen in these crewmembers will become more diverse. Consequently, a means of assessing which physiological changes should be considered abnormal and which should be considered normal is an important consideration in determining crew health and function. Because of the fact that

assessing crew health requires a quantitative understanding of the changes that occur during zero gravity, part of this contract was devoted to an integration of preliminary systems hypotheses, developed in contract NAS9-14523, into a whole-body definition of health in space and to continue research in each physiological system to develop further the definition of health in space.

Once a definition of health in space was established, suitable criteria would need to be developed to detect abnormal states. Up to this point in time, space-flight data and experience have been insufficient to allow one to assign "health" ratings to space-flight crewmembers. In the absence of such data and experience, certain physiological parameters were identified tentatively for their use as criteria in the prediction of health status. The potential inherent in the use of systems analysis in such a manner was demonstrated by performing a successful stand-alone simulation (no contact with the investigators) of the joint US-USSR 5° head-down tilt bed rest study. Such a demonstration clearly indicates that a full automated health-monitoring system, capable of determining zero-g health status, is a real possibility.

A major undertaking during this contract was the writing of a NASA Reference Publication (NASA-RP) titled An Integrated Analysis of the Physiological Effects of Space Flight. This NASA-RP contains the most current and complete evaluation of changes observed or suggested in the fluid and electrolyte, thermoregulatory, cardiovascular, hematological, and musculoskeletal systems. These major systems are developed individually, and when possible, integrated into a whole-body system. The data base, analysis tools, and supporting experimental and simulation analogs, from which the space-flight hypotheses were developed, are discussed, as are assumptions and gaps in the analysis. Consequently, the NASA-RP is a thorough discussion of health in space, as it is currently understood. It also contains the systems analysis background that went into that understanding. As such, the NASA-RP is a document that covers portions of all of the tasks in this contract.

All of the studies, analyses, model modifications, and model developments performed under this contract have been reported in GE Technical Information Releases (TIR's) or in the NASA-RP mentioned above. This latter document, which represents a detailed summary of many years of work, is not completed at the present time, but should be available within a few months. It will be cited throughout the main body of this final report. Furthermore, since this project is integrative by its very nature it is impossible to sharply divide one task from another. There is much overlap and many of the studies and analyses performed were strongly related to more than one subtask.

Section 2.0 of this report summarizes the work done under each contract task and identifies those documents which describe the detailed work done and the major results obtained. Section 3.0 contains the main conclusions resulting from the contract, while section 4.0 presents recommendations for future studies.

Appendix A presents a complete listing of all documentation comprising this final report. Appendix B provides an outline for the NASA-RP in preparation. Appendices C and D present ordered lists of the documentation items.

2.0 TASK DESCRIPTION AND CONTRACT PERFORMANCE

In this section, the original task items are reviewed and the work performed under each item is summarized. Appendix A contains a complete list of all published papers and technical reports which elaborate on the items summarized here and all of these documents should be considered an integral part of this final report. This approach is used in order that the strong relationships between the task items and the work performed is exhibited clearly.

2.1 (TASK 5.1) DEFINITION OF ADVANCED HEALTH MONITORING TECHNIQUES

Because exposure to weightlessness causes physiological adaptation, the definition of "normal" health must change as man enters and departs from the weightless state. Skylab experiments have provided enough information to permit a preliminary definition of health in space, at least in terms of anticipated basic physiological changes. It appears reasonable to assume that if such "performance criteria" for zero-g health can be established, an automated system could be defined to help address many health related problems which will appear as man's travel into space continues and expands. Such a system could be used as a health monitoring system.

On previous space flights, a classical health monitoring approach has been used because of the many uncertainties of space flight. The main objective of this task was to determine guidelines necessary to improve or replace the classical health monitoring approach with an automated system for use on the Space Shuttle missions. Improvements were to include reducing the number of required procedures performed, developing new performance indices, and automating other procedures to provide preprocessed, summarized, near real-time crew health profiles.

In order to achieve these goals, it was necessary to address the following subtasks:

- 1) Zero-g health should be defined as it relates to the Shuttle crews, taking into consideration that, on the Shuttle, there will be more flights, less time between flights, and that

crew and passenger population differences from previous astronauts may result in a higher probability of illness or injury.

- 2) In order to assess crew health at any point in time and to provide indicators of future health, the use of computerized simulation models and other systems analysis techniques should be included.
- 3) Previous monitoring procedures should be studied to see if they can be eliminated and/or automated to provide optimum health monitoring, with a minimum of measurements and work by the crewmembers.

2.1.1 State-of-the-Art Survey of Automated Health Monitoring Techniques

The objective of this subtask was to review automated health monitoring systems currently in use in health care facilities to determine if parts or all of these systems could be adopted for a Shuttle Health Monitoring System. By integrating monitoring systems previously developed for space missions with new monitoring equipment and data processing techniques, candidate equipment was to be identified and developed.

Only two systems, the Integrated Medical and Behavioral Laboratory Measurement System (IMBLMS) and the Space Technology Applied to Rural Papago Health Care (STARPAHC) system were found suitable for use during space flight. These were found to be technically feasible as well as cost-effective and could easily be adapted to space flight. These systems are not fully automated at present. However, the trend of internal microprocessor control in clinical instrumentation should easily permit modification of off-the-shelf equipment for use in either of these systems. Further details and considerations for automated systems and requirements may be found in TIR 741-LSP-9022, "Requirements for an Automated System to Monitor Crew Health."

2.1.2 Candidate List of Physiological Parameters

The objective of this subtask was to develop a list of physiological parameters capable of describing zero-g health, including the parameters necessary to evaluate stress test indices, as well as countermeasure techniques, and therapeutic measures.

This subtask was satisfied by a study report entitled "A Prioritized Set of Physiological Measurements for Future Space-Flight Experiments," released as TIR 741-LSP-8033. The objective of this report was to identify the human physiological measurements which should be made in the upcoming Shuttle space-flight experiments. The relative importance of each measurement was expressed as a category, or priority. The basis for identifying the measurements was the physiological systems analysis performed on Skylab data and related ground-based studies. A prioritized measurement list was developed for each of the following areas: cardiopulmonary, fluid-renal-electrolyte, hematology, immunology, and musculoskeletal. Also included was a list of interacting stresses and other factors of space flight whose effects it may be necessary to quantify. A set of criteria and an overall approach for prioritizing the measurements were identified and discussed through the use of examples.

2.1.3 Sensitivity of Measured Physiological Parameters

The objective of this subtask was to apply, wherever possible, sensitivity and error analysis techniques to simulation models as well as to their associated parameters in order to determine minimum acceptable sensitivity and overall system accuracy requirements. Part of this subtask was fulfilled by TIR 741-LSP-8012, entitled "Study Report: Statistical Considerations in Design of Spacelab Experiments" and by Appendices E and F of the NASA-RP "An Integrated Analysis of the Physiological Effects of Space Flight." The report TIR 741-LSP-8012 presented an analysis of the sources of experimental error. The relation of these errors to number of subjects, number of replicate measurements, and number of daily measurements were

presented in a general form, using dimensionless equations and graphs. These results are useful for determining approaches to reduce experimental error and establish minimum sample size. The last portion of the report was a discussion of the statistical aspects of several biomedical experiments proposed for the Space Shuttle, including: determination of bone density by computer tomography, determination of basal metabolism, and measurement of total body water. A description of error analysis techniques and their application to the metabolic balance studies can be found in Appendix F of the reference publication previously mentioned.

This subtask was satisfied also by the preparation of Appendix E of the same reference publication. This work, which was initiated under a previous contract, was modified and updated to present a description of a general sensitivity analysis for biomedical simulation models, and to present an application of sensitivity analysis to the thermoregulation model in particular. Sensitivity analyses were also performed in conjunction with the cardiovascular and erythropoiesis models, details of which can be found in TIR 741-LSP-9005, "Dynamic Regulation of Erythropoiesis: A Computer Model of General Applicability," an article written by Leonrd et al., 1979: "Computer Simulation of Erythropoiesis Suppression in a Potential Animal Model for Space Flight," as well as in the reference publication.

2.1.4 Modeling Approaches for Predicting Physiological Indices of Health

The objective of this subtask was to investigate the use of simulation models to accurately predict difficult-to-measure physiological parameters which may determine new indices of zero-g crew health.

This task was satisfied by the following:

- 1) TIR 741-LSP-8023, "Study Report: Development of an Hypothesis for Simulating Anti-Orthostatic Bed Rest;"
- 2) TIR 741-LSP-9016, "A Numerical Method for Solutions of Systems of Stiff Differential Equations: the Hybrid Euler Integration Technique;"

- 3) a paper by Leonard, Leach, and Rummel, 1979 entitled "Computer Simulation of Postural Change, Water Immersion, and Bed Rest: An Integration Approach for Understanding the Space-Flight Response;" and
- 4) TIR 741-LSP-9023, "Erythropoiesis Teaching Model."

The first technical information release mentioned above, 741-LSP-8023, described the modifications made to the existing Guyton model. These modifications included leg compartments and the effects of a gravity vector, making it possible to simulate anti-orthostatic studies, and to evaluate hypotheses describing leg dehydration and fluid shifts. It is important to consider these modifications, since many significant changes that are observed during space flight and bed rest can be attributed directly or indirectly to reactions initiated in the legs and their fluid and tissue compartments. These include: 1) the fluid shifts from vascular and extravascular compartments resulting from altered hydrostatic gradients; b) the degradation of musculoskeletal tissue function as a result of reduced gravitational loading forces on the tissues and their proprioceptors; and c) the altered metabolic function in many body tissues and organs, including the legs, as a result of reduced physical activity (observed in bed rest, but unconfirmed in Skylab). It appears that these disturbances, none of which are completely understood, are of such fundamental nature that they can affect circulatory, renal, hormonal, and metabolic function, not only in the acute state, but also for much longer periods of time.

Technical information release 741-LSP-9016 described a technique which allows a faster solution to be calculated for certain differential equations. Therefore, steady-state results can be computed more quickly and more cheaply and this, in turn, allows sensitivity coefficients to be calculated with similar savings of time and money.

This technique has been incorporated into the erythropoiesis model. Technical information release 741-LSP-9023 described how

the modified model was used to formulate a teaching model. The teaching model predicts health status by combining gross physiological attributes (as can be determined from physical exams) with a mathematical model of erythropoiesis.

The paper by Leonard et al., 1979, demonstrated how short-term and long-term fluid and electrolyte experimental results from simulation studies can be integrated to yield an understanding of the physiological responses to space flight. The simulation model described in the paper can be used to help predict the status of the crew's health, with respect to body fluid and electrolyte parameters.

2.1.5 Physiological Criteria for Zero-g Health

The objective of this subtask was to develop physiological criteria that will define the current status of crew health and detect physiological changes during space flight. These criteria were to be based upon quantitative indices. These indices were to include traditional resting health parameters as well as more integrative indicators of crew health (such as water and electrolyte balances).

This task was satisfied by the NASA-RP An Integrated Analysis of the Physiological Effects of Space Flight. An extended outline of this publication is provided in Appendix B of this final report. Details of the analyses provided in the reference publication and their relation to the contract can be found under the appropriate tasks and subtasks in this report.

The reference publication mentioned above describes an integrated analysis of the human physiological response to weightless space flight and presents the results of this analysis. This work spans seven years of effort by many NASA investigators and contractor personnel working under three major NASA contracts (NAS9-12932, NAS9-14523, and NAS9-15487) and several smaller contracts. Parts of this work, the results of all the experiments involved, and the results of many of the analyses performed in each investigative area,

have been published in various journals or given orally as presentations, or documented in contractor reports. The intent of this reference publication was not to reproduce these documents and publications, but rather to present the integrated analyses under one cover. The integrative aspect of this work was unique to this project and could only be presented in a forum where the entire scope of the project could be covered.

While the results of this analysis do not present a definitive treatise of all the physiological changes associated with exposure to the space-flight environment, they do represent the most integrative and systematic overview of physiological adaptation to weightlessness available to date. Another unique aspect of this work, in the context of the analysis of physiological experiment results, was the use of systems analysis as the basic approach to the problem. This publication, therefore, not only provides the results of this project, but it also describes the unique approach and the tools and techniques developed to implement this approach.

The primary areas of investigation in this project were 1) fluid, electrolyte, and hormonal; 2) cardiovascular and pulmonary; 3) hematology; and 4) body composition, calcium regulation, and metabolism. Summaries of the pertinent space-flight and related ground-based experiment results, proposed hypotheses, and unanswered questions in these areas were all presented in the reference publication together with the systems analysis approach and the tools and techniques developed to implement this approach. These tools included the development of a data base and analysis system for storing, manipulating, analyzing, and graphically displaying the experimental data simultaneously with simulation model output, as well as development of mathematical formulations to synthesize system functions. These latter formulations range from simple balance equations, to complex models of physiological control systems. Simulation models were used successfully in each investigative area, particularly in developing and testing individual subsystem hypotheses. These models were also grouped into what is

termed the "whole-body algorithm" for the integrated analysis. The whole-body algorithm was validated and used to develop and test hypotheses involving more than one investigative area. Ultimately, the whole-body algorithm was used to develop an integrated hypothesis which describes the best understanding of physiological adaptation to space flight to date. Mathematical models also were used to estimate or infer experimental data which could not be measured directly, and to simulate the systems response to an imposed stress.

Many questions have been answered during the course of this work and many more have been posed. The full potential of this approach can only be realized when there is a close association between experimental investigation and systems analysis. It is this iterative process of experimentation and analysis that points the way to new investigation. In the reference publication, a section is provided which discusses the planned and potential uses of systems analysis in current and future programs. This section describes the uses of the approach and analysis systems developed in this project for designing new ground-based and flight experiments for the Shuttle era.

2.1.6 Transfer of Programs and Data Bases from the Univac 1110 to the DEC

The objective of this subtask was to transfer the current project programs and data bases from the Univac 1110 to the PDP 11/40 computer, in order to provide near real-time data analysis and trend predictions.

The integrated data base and analysis system as well as all of the physiological simulation models were moved from the Univac 1110 to the PDP 11/40. The data bases and programs have been reformatted for the PDP and are stored on permanent disks. All of the subroutines have been recompiled and checked for errors. Resegmenting of the programs and overlay programming were necessary in order to collect all the subroutines for any program in the limited core available. It was found that the Tektronix graphic library did not

have source programs available to be recompiled. The library was transferred from the Univac 1110 and made operational on the PDP 11/40.

2.2 (TASK 5.2) COMPUTER SIMULATION OF ERYTHROPOIESIS

The overall purpose of this task was to study the physiological control of erythropoiesis in the context of understanding red-cell loss observed during space flight. The most important systems analysis tool available for this application was a computer simulation model of erythropoiesis regulation, developed previously by this contractor (under contracts NAS9-12932 and NAS9-14523). This model represented a unified framework to integrate ground-based and space-flight studies. Simulations with this model provided a systematic procedure for identifying important research areas, formulating and evaluating hypotheses, and assisting in experiment design and interpretation of results.

The objectives of this task, as outlined in the statement of work, relate to: a) applying the existing model to newly acquired data; b) developing a new model capable of simulating erythropoiesis in an animal species; c) improving the existing model, if necessary, based on limitations uncovered in the simulation studies; d) adapting the present human model for instructional purposes; and e) integrating the hematological results and hypotheses relating to space flight with other major physiological systems. These will be discussed below.

2.2.1 Application of the Existing Erythropoiesis Control Model

The purpose of this task was to apply the simulation model to design experiments and to use the model to interpret experimental data in conjunction with ongoing ground-based studies. In this manner, the simulation model would serve as a focal point for integrating diverse types of research related to space-flight disturbances of the erythropoietic system.

A reduction of red cell mass, with a concurrent reduction in plasma volume, has been a consistent observation in both short and long duration flights. Hyperoxia, which was generally believed to have contributed to the early death of red blood cells on the Gemini and Apollo flights was not a factor in the Skylab missions. Instead, it appears that suppressed erythrocyte production at the bone marrow level was responsible for the loss in red cell mass, although no conclusive proof of this is available and no one mechanism has been identified which is consistent with all the data. Earlier studies by this contractor, in conjunction with the simulation model, demonstrated that hemoconcentration, observable early in space flight, could provide an appropriate stimulus for suppressing the sensitive renal-bone marrow control axis. During this contractual period, this and other hypotheses were examined in the light of newly acquired data. Specifically, the following work was accomplished:

- 1) A significant achievement was the development of an interactive relationship with an ongoing experimental hematology program. Dr. C.D.R. Dunn (University of Tennessee) has been studying (under NASA auspices) the "anemia" of space flight using experimental animals and various experimental models such as dehydration and infusion. Dr. Dunn, in the capacity of Visiting Scientist and in the employ of the contractor, devoted eight weeks at JSC to becoming familiar with the computer model and associated simulation techniques. He was also instrumental in establishing requirements for the animal model which was being developed concurrently. The contractor subsequently transferred a copy of the model to the University of Tennessee's computer facilities for Dr. Dunn's use. During the following period, Dr. Dunn initiated a series of experiments that validated the mouse model and tested a number of hypotheses which were explicitly suggested by the model simulations. The contractor supported this work directly and complemented it by performing simulations of Dr. Dunn's experiments. The iterative nature of this work, cycling between simulation and experimentation,

provided many valuable insights into the possible mechanisms of the red blood cell mass loss related to space flight. The work of this task was summarized in TIR 741-LSP-8029, "Research Report: Use of a Computer Model in the Understanding of Erythropoietic Control Mechanisms," by Dunn et al., 1979, and by Leonard et al., 1979.

2) As a result of the foregoing studies, the Skylab data were re-examined with computer simulation and data analysis techniques. The hypotheses tested included those related to: a) hemoconcentration, b) negative energy balance, c) hemolysis and d) regeneration of cells during flight. In general, the effects of hemoconcentration (resulting from plasma volume loss) and negative energy balance (resulting from restricted dietary intake) appeared to be consistent with observed results. The other hypotheses appeared less plausible, but suggestions were offered to test their veracity with more definitive flight experiments. These results have been summarized in the hematology subsection of the NASA reference publication An Integrated Analysis of the Physiological Effects of Space Flight, which is in preparation at this time.

3) An earlier study performed by the contractor was submitted and subsequently published by Kimzey et al., 1979. This study compared bed rest results with the hematological observations from space flight as well as with the simulation results of the erythropoiesis model.

4) A study which compared the differences between relative and absolute polycythemia was completed. Relative polycythemia (hemoconcentration resulting from a decrease in plasma volume) can be experimentally induced by bed rest, dehydration, and space flight, while absolute polycythemia is achieved by infusion of red cells. The computer model originally was not capable of distinguishing between these stresses. However, data gathered from both human and animal studies suggested some important differences. A set of hypotheses was developed and successfully tested in the modified model that more closely simulated the experimental responses. These

studies were important in establishing appropriate experimental ground-based maneuvers for investigating the loss of red blood cells in space flight. The results of this study were presented at a scientific meeting and submitted for publication (Dunn et al., 1979; Leonard et al., 1979; and Kimzey, 1979).

2.2.2 Feasibility Study for Developing a Species Specific Model of Erythropoiesis

The purpose of this task was to develop a species-specific simulation model suitable for analyzing results from studies using experimental animals (primarily the mouse or rat). This new model was to be based on the existing model which is primarily a human model, but which had the capability of being modified to include the appropriate rate functions and scaling factors to represent the species of choice.

A preliminary study identified a number of parameters that would be required to convert the human mathematical model to an animal model. A thorough literature survey was completed to determine these parameter values for the rat and mouse. Values that were missing from the literature were assumed to be based on other species or were obtained by logical deductions from animal experiments. The results of this study were summarized in TIR 741-LSP-8024, "System Parameters for Erythropoiesis Control Model: Comparison of Normal Values in Human and Mouse Model." On the basis of this survey and current research needs, the task monitor directed the contractor to develop a model for the mouse (although the original Statement of Work called for a rat model). While the contractual obligations were limited to a feasibility study, the results appeared so promising that a working model was developed, implemented, and validated. The application of this model to ground-based experiments is described in this report in sections 2.1 and 2.3.

2.2.3 Improvements to the Erythropoiesis Control Model

The purpose of this task was to continue efforts to improve the fidelity and utility of the model by incorporating changes in

model structure and its associated software. The following work satisfied this objective.

1) Improved input/output software was developed to provide user convenience during simulations and to incorporate experimental results into the simulations. This work was documented in TIR 741-LSP-8004, "User's Instructions for the Erythropoiesis Regulatory Model."

2) An improved numerical integration algorithm was incorporated into the erythropoiesis model which increased the solution speed by a factor of 100 to 1000. This capability permitted simulations to be accomplished much more rapidly, and it should prove even more advantageous in case the model is programmed on smaller computer facilities. A dynamic interrupt mode of operation was also installed to permit parameter changes to be made at any time during simulation execution. The documentation of these modifications can be found in TIR 741-LSP-9016, "Numerical Methods for Systems of Stiff Differential Equations: The Hybrid Euler Integration Technique."

3) A more generalized algorithm for the computation of oxygen saturation of hemoglobin based on the oxy-hemoglobin equilibrium curve was formulated and implemented. This formulation should permit different species to be represented in the model more efficiently than in the original algorithm, which was designed primarily for human blood. Documentation can be found in TIR 741-LSP-8024, referred to previously.

4) The effect blood volume and blood viscosity changes have on blood flow and oxygen delivery was reviewed and summarized in the previously mentioned NASA reference publication. Hypotheses regarding these effects on erythropoiesis during infusion and dehydration polycythemia were tested in the model and documented in Leonard et al., 1979, and in TIR 741-LSP-9005, "Dynamic Regulation of Erythropoiesis: A Computer Model of General Applicability."

5) The basic model for human application with the more recent modifications was fully documented, at the request of the task monitor, and submitted to a clinical journal for consideration for publication. Publication of simulation results has been hampered in the past by the unavailability of a good model description.

2.2.4 Development of a Teaching Model from the Current Model of Erythropoiesis

Using a simulation model for instructional purposes is a relatively new endeavor, although some effort in this area has been made for nearly ten years. It was recognized that the erythropoiesis regulatory system, in spite of its simplicity, was associated with a large number of pathologies and that a model of this system might be useful to further demonstrate the educational benefits of computer simulation. The purpose of this task was to develop a teaching model suitable for assisting biomedical students in the study of the pathophysiological behavior of a selected group of hematological disorders.

An initial study was completed that resulted in a list of requirements for the teaching model. Briefly it was designed to present the medical student with a set of symptoms and clinical conditions and provide the computer capability to respond to user inquiry in formulating a preliminary diagnosis. The model should be capable of iterating between treatment and diagnosis to study the course of a disease in advanced stages and to discern the effects of the treatment on the course of the disease. A category of anemias was chosen as the group of disease states for study.

This candidate approach was extended into the design stage by developing an attribute function model to be used in conjunction with the mathematical model of the physiological system. Approximately 60 attribute parameters were identified to represent the "medical state." These parameters included such aspects as sex, age, race, level of oxidant stress toxins, family history of hemolytic disease, and level of glucose-6-phosphate dehydrogenase activity. The medical state defined in this manner was analogous to the "physiological state" defined by the feedback control using

such physiological parameters as erythropoietin plasma levels, hematocrit, red cell production rate, and oxy-hemoglobin affinity. The medical parameters were divided into logical groups related to the medical history of the patient, a physical examination, and a laboratory examination. Each disease state was described by a unique set of attribute parameter values, which would be available to the student user upon his or her request for specific information. A unique mapping technique was formulated that allowed the medical parameters to determine the physiological parameters. In this manner, the medical parameters could be altered by a simulated medical treatment and thereby influence the physiological parameters. The actual course of the disease under treatment was determined by the dynamic simulation of the mathematical model under the control of the physiological parameters. Implementation of this approach was accomplished by developing the software for describing the attribute, examination, diagnosis, and treatment functions. Final implementation must await further definition of the specific mapping functions and assignment of discrete values to the attribute parameters. Documentation of the teaching model's development is described in TIR 741-LSP-9023, "A Teaching Model for the Erythropoiesis System."

2.2.5 Systems Analysis to Define Interrelationships Between Selected Zero-g Observations

The purpose of this task was to apply systems analysis techniques to study the interrelationships between the erythropoietic system and other major physiological systems in the face of hypogravic stress. In addition, summaries of the hypotheses used to account for the major hematological changes observed in space flight were to be prepared.

This objective was satisfied by two efforts. The first effort, the NASA reference publication entitled An Integrated Analysis of Physiological Effects of Space Flight examined the systems analysis of erythropoiesis in space flight. A major

section of this manuscript was devoted to summarizing the most relevant data of the manned space-flight program, developing a theoretical basis to account for these results, summarizing all hypotheses used in the analysis, and describing the simulation studies accomplished under this and the previous two NASA contracts with this contractor. A portion of the reference publication manuscript also discussed the interrelationships of the oxygen transport-blood forming system with other physiological systems. Factors such as changes in plasma volume, diet, and exercise were suggested as being responsible for the decrements in red cell mass, as well as playing a major role in the fluid-electrolyte regulation and orthostatic responses of the cardiovascular system. Documentation of this task is described further in section 2.1. A second effort in integrating the results of the erythropoiesis modeling project was performed by providing support to the task monitor in preparing Kimzey et al., 1979.

2.3 (TASK 5.3) DEFINITION OF CHANGES AND CONTROL MECHANISM IN FLUID AND ELECTROLYTE METABOLISM

A working hypothesis of the systems analysis effort has been that shifts in fluid volumes and electrolytes which occur as a result of weightlessness can explain, in large measure, the observed changes in renal, cardiovascular, and hormonal responses both at rest and in the performance of provocative metabolic and orthostatic stresses. Accordingly, an important aspect of the entire systems analysis project has been devoted to accounting for fluid-electrolyte regulation during space flight and of determining the interrelationships between this and other physiological systems. The foundation for this work was established during previous contractual efforts (NAS9-12932 and NAS9-14523) and is summarized in TIR 741-LSP-7020, "Final Report on Contract NAS9-14523." The focus of the present contract period was on two aspects of systems analysis: a) simulation studies using the circulatory, fluid, and electrolyte regulatory model; and b) analysis of body composition data

integrated metabolic balance analysis algorithms. Both of these approaches involve a high level of integration of either regulatory mechanisms or space-flight data.

2.3.1 Simulations of Short Term Fluid-Regulatory Responses

The purpose of this task was to examine, using simulation techniques, the onset of weightlessness (i.e. short-term effects). Experimental data were to be obtained from space flight, head down bed rest, and water immersion studies. Where necessary, the model of Guyton could be modified to more realistically simulate the stress of interest. The following work was accomplished under this task:

1) A summary of space-flight simulations was prepared by Leonard et al., 1978. This presentation pointed out the fact that most of the fluid-electrolyte space-flight data were obtained relatively late in flight, after most of the significant changes in fluids and electrolytes had occurred. This suggested that a study of short-term, ground-based experiments such as bed rest and water immersion would prove valuable in better understanding the early response.

2) Water immersion is an excellent method for inducing acute shifts of fluid from the legs to the upper body. Data from studies using this method are abundant, but each study tends to focus on different aspects of cardiovascular, hormonal, renal, fluid, or electrolyte responses. One of the accomplishments during this contract period was the assembling of these data into a composite picture of the physiologic response to water. Simulations were accomplished which closely agreed with this combined data. The effects of dehydration on the immersion response were also studied by computer simulation. These results help to explain the lack of an observed diuresis in the Skylab crew. These results were documented both in summary form (by Leonard et al., 1979) and in detail (in the NASA reference publication, An Integrated Analysis of the Physiological Effects of Space Flight).

3) A study was undertaken to simulate head-down tilt. This is a relatively new method for experimentally simulating the fluid shifts of space flight. Modifications to the Guyton model were required in order to provide a realistic representation of the collapsible nature of leg veins. Simulations were performed of the headward fluid shifts and the accompanying neutral-hormonal-hemodynamic response using data from two head-down tilt studies. One of these included the joint US-USSR bed rest study performed at NASA-ARC. Model agreement with observed data was good and the simulation study suggested a group of measurements that would be desirable in future experiments both in space and on the ground. Results of these studies are available through the reference publication mentioned above, and were released through TIR 741-LSP-8023, "Study Report on Development of an Hypothesis for Simulating Anti-Orthostatic Bed Rest," and by Leach, 1979.

2.3.2 Integrated Systems Analysis of Fluid-Electrolyte Responses

The purpose of this task was to develop an integrated understanding of the process of physiological adaptation to the zero-g environment. This was to be accomplished, in part, by summarizing observations and hypotheses for the fluid-electrolyte investigative area as it related to the Skylab biomedical program. Where necessary, new data analyses were to be performed. These objectives were satisfied by the following work:

1) Data relating to body composition changes were collected extensively during the Skylab program. An analysis was accomplished to integrate this data by using four distinct and independent methods to compute lean-body mass and body fat changes resulting from space flight. These methods were based on body water, body potassium, nitrogen-potassium balances, and body density data. The results of this study were fully documented in TIR 741-LSP-9017, "Quantitation of Tissue Loss During Prolonged Space Flight."

2) Changes in body composition (losses of water, muscle, and fat) are relatively dramatic during space flight. The dynamics

of these processes were not quantitatively known, although data from Skylab were available that could provide this information. An extensive data analysis procedure was developed (Integrated Metabolic Balance Analysis) to process the voluminous quantity of metabolic balance data. These algorithms were based on unique formulations which combined water balance, mass balance, electrolyte balance, and energy balance, as well as whole-body measurements of mass and water. The result of this analysis was a quantitative description of the changes in body mass, body water, body fat, and body protein as a function of time spent in space. The results were applied to defining caloric and exercise requirements during space flight. This study was documented in the presentation by Leach, 1979, and in TIR 741-LSP-9021, "Energy Balance and the Composition of Weight Loss During Prolonged Space Flight."

3) The entire body of information relating to the systems analysis of body fluid-electrolyte regulation which has been accomplished during the last seven years has been summarized in the previously mentioned NASA reference publication. This includes: the integrated metabolic balance analysis (water balance, evaporative water loss, potassium and sodium balance, energy balance, and body composition changes), simulation of studies (space flight, supine bed rest, head-down bed rest, water immersion) and regulatory feedback mechanisms (circulatory, renal, endocrine, and fluid-electrolyte systems). In addition, a succinct summary of the fluid-electrolyte data obtained from the Skylab subjects was prepared, including a new analysis of nine-man average endocrine responses. Hypotheses which attempt to account for these observations are included also, along with the supporting simulations or data analyses. An important contribution of systems analysis has been the integration of short term and long term responses to weightlessness, as documented by Leonard, 1979. The effect of the fluid-electrolyte regulatory mechanisms on other physiological systems is also discussed in the NASA reference publication An Integrative Analysis of the Physiological Effects of Space Flight.

2.4 (TASK 5.4) INTEGRATED ANALYSIS OF MUSCULOSKELETAL CHANGES

The objective of this task was to provide an integrated analysis of ground-based and inflight experiments which relate to changes in musculoskeletal function observed during space flight. The most important area of concern was the unabated loss of calcium. However, the muscular and skeletal systems of the body function as integrated systems and both seem to be affected by the lack of weight-bearing stimuli during bed rest and zero-g studies. Consequently, atrophy of muscle and skeletal tissues, both of which are commonly observed during long-term hypogravic stress, were examined.

The performance of this task evolved around techniques which had been developed under a previous NASA contract (NAS9-14523). These techniques included a data base as well as analytic software, metabolic balance computer programs, and familiarity with the performance of systems analysis of physiological systems. The systems analysis involved integrating ground-based and space-flight data, as well as translating the physiological systems into simulation models. The objectives of this task were satisfied by three subtasks, which included:

- 1) an overall systems analysis of musculoskeletal physiological regulation;
- 2) a space-flight data analysis and integration; and
- 3) an integration of bed rest data and space-flight data.

2.4.1 Overall Systems Analysis of Physiological Regulation

The first subtask involved systematically identifying the elements associated with calcium regulation and with determining the physiological interactions between those elements. The space-flight investigative program of the musculoskeletal changes yielded a variety of possible mechanisms which were possibly involved in the disturbances to the system. This task was aimed at understanding both overall calcium regulation and the potential role of each of the

mechanisms recognized in the space-flight program. Consequently, this subtask was divided into four sections: a literature review of pertinent systems; a description of calcium metabolism in the normal adult; an identification of potential disturbance points within the musculoskeletal system during hypogravic stresses; and a preliminary design for a mathematical, computer simulation model of calcium regulation.

Literature reviews were performed which examined overall calcium metabolism, bone metabolism, and particular factors related to calcium and bone regulation. Calcitonin, parathyroid hormone, Vitamin D, phosphate, and stresses resulting in piezoelectric effects were the specific regulators reviewed. The kidney (for excretion), the intestinal tract (for absorption), and the bone (for storage) were the specific organs that were reviewed. A literature review of the relationship between the skeletal and muscular system during bed rest was performed as well. A brief review of exercise as a countermeasure to the space-flight muscular and skeletal losses was included within the review of the two interacting systems. Finally, a review of the musculoskeletal results from the Gemini, Apollo, and Skylab programs was performed.

Some of the reviews listed above were published as technical information releases (TIR's). The review of the space-flight calcium studies was published in TIR 741-LSP-8015, entitled "A Brief Review of Space-Flight Calcium Metabolism: Results and Methodologies." The report entitled "Study Report on the Influence of Exercise on Bone Atrophy" (TIR 741-LSP-8011) reviewed the relationship between the skeletal system, the muscular system, and exercise. The only other reviews published were those of calcitonin and parathyroid hormone. The calcitonin review was entitled "Study Report: The Role of Calcitonin in Calcium and Bone Metabolism" (TIR 741-LSP-9004). The parathyroid hormone review is found in TIR 741-LSP-9024, "The Parathyroid Hormone Subsystem Model."

Diagrams and flowsheets were prepared to describe the regulation of calcium, phosphate, parathyroid hormone, vitamin D, and calcitonin, as well as the regulation of intestinal calcium absorption and calcium metabolism. Equations were written describing the secretion rate and plasma concentrations of parathyroid hormone and calcitonin. Equations were written also describing the metabolism of Vitamin D and the intestinal absorption of calcium. These mathematical relationships have been implemented on the Univac 1110 computer. The parathyroid equations are also available in TIR 741-LSP-9024, entitled "The Parathyroid Hormone Subsystem Model."

The reviews also led to the identification of known or potential disturbance points within the calcium regulatory system which, in turn, might provide clues to the observed space-flight results. The technical information releases entitled "Study Report on a Double Isotope Method of Calcium Absorption" (TIR 741-LSP-8009) and "Strontium Metabolism in the Rebuilding of Skeletal Tissue" (TIR 741-LSP-8010) focus on two of the potential disturbance points. These and other critical areas were discussed further in a Spacelab experiment proposal, to which the contractor contributed extensively. Contributions include "A Study of Bone Loss in Weightlessness," and a NASA reference publication entitled An Integrated Analysis of the Physiological Effects of Space Flight, which is still in preparation.

The last part of this subtask required a preliminary design for a computer simulation model of calcium regulation. A list of objectives, requirements, and guidelines was developed for a calcium model and can be found in TIR 741-LSP-8022, "Preliminary Design Specifications of a Calcium Model." A survey of existing models also is located in the TIR. The existing models were evaluated in relation to the objectives and requirements of the desired model. All of the existing calcium models fell short of the desired objectives and requirements. Consequently, the development of a computer simulation model of calcium metabolism, based upon the preliminary design specifications, was initiated.

Before the end of the contract period, subsystem models of parathyroid hormone, calcitonin, vitamin D, and intestinal calcium absorption were implemented on the computer. Validation was accomplished for the parathyroid hormone system. Two of the subsystem models were presented at the 32nd Annual Conference on Engineering in Medicine and Biology. Abstracts of the two models, entitled "A Mathematical Model of the Parathyroid Gland" and "A Mathematical Model of Vitamin D Metabolism" were published in the proceedings of the conference.

2.4.2 Space-Flight Data Analysis and Integration

The purpose of the second subtask was to provide systems analysis and data integration support to the task monitor as required. This support included reviewing, summarizing, graphing, and tabulating the results of space-flight experiments related to the musculoskeletal system, completing the analysis of mineral balance data, and performing an integrated data analysis.

A review and summary of the space-flight musculoskeletal experiment results can be found in TIR 741-LSP-8015. Further analysis and integration was done in support of the task monitors by providing assistance in the planning of future experimental work.

2.4.3 Integration of Bed Rest Data and Space-Flight Data

The third subtask involved the integration of data from ground-based and space-flight studies. This task was to depend, largely, upon the results of the previous subtasks, the incorporation of bed rest data onto the computer, and the requirements of the task monitor. Data from the U.S. Public Health Hospital in San Francisco bed rest studies were entered into a data base for data analysis and used in validation of the completed calcium model. The sets of bed rest data represent 12 years of research by the U.S.P.H. group, presently under the direction of Dr. Victor Schneider. The data sets were composed of 20 separate bed rest studies conducted in the hospital. The data were in the form of

data sheets, which were copied from Dr. Schneider's notebooks. A data structure for the computer was developed and eight of the bed rest studies were entered into the computer. Preliminary statistical programs were also written and incorporated into the computer. The programs were designed to treat any parameter in the computer files. The statistical package included data averages and standard deviation of a single subject within a single study or each phase of the study, multiple subjects within a single study or each phase of the study, and the balance data of a single subject. Two of the statistical programs and six of the bed rest studies are fully operational. The results of this work can be found in TIR 741-LSP-9019, entitled "User's Guide to Bed Rest Statistical Analysis Program."

The existing Skylab Medical Data Evaluation Program (SMEDEP) data base contains data in combination with the bed rest data base (described above), and provides the basis for a fully automated integrative analysis of ground-based and space-flight studies. Although this integration has not yet been accomplished in a quantitative manner, a discussion of this type of data has been included in the reference publication.

The net result of Task 2.4 was the design and partial development of a mathematical computer simulation model of calcium regulation, preliminary hypothesis development of the unabated losses of calcium during space flight and ground-based analogs, and preliminary data analysis and integration of zero-g and ground-based experimental results.

2.5 (TASK 5.5) DETERMINE SIMULATION MODEL AND DATA ANALYSIS SYSTEMS REQUIREMENTS AND SPECIFICATIONS TO SUPPORT CREW HEALTH MONITORING FUNCTIONS

The objectives of this task were: 1) to develop a real-time system of data analysis and decision-making aids to insure the safety of the crew and the success of the mission, and 2) to acquire detailed biomedical information on man's abilities and

limitations in space, as well as his characteristic reactions to weightlessness. The biomedical information obtained was used to insure the safety of the crew.

To fulfill these tasks, the requirements and specifications were developed for an automated system which would perform an integrated analysis of the physiological, clinical, and special experimental monitoring systems. By using compatible inflight and ground-based systems, the raw data could be automatically processed, cataloged, and displayed, and long term and acute abnormal function could be detected.

The task was satisfied by TIR 741-LSP-9022, entitled "The Requirements for an Automated System to Monitor Crew Health." The primary problems in assuring crew health were to define health in zero g, remotely examine the crew, automatically analyze and store the data, and rapidly detect pathological changes. The report discusses the difficulties and requirements involved in developing an automated system to perform these functions.

The definition of health in zero gravity has been difficult because of the limited understanding of how fundamental physiological processes operate in zero g. Most of what has been learned concerning the physiological effects of weightlessness came from the Skylab studies. The results of the experiments conducted aboard Skylab and the results of model simulations have added greatly to the understanding of the physiological responses to weightlessness. The largest compendium of this knowledge, which was completed for this contract, will be found in the NASA reference publication Integrated Analysis of the Physiological Effects of Space Flight. This publication is presently in preparation.

Remote examination of the crew and the delivery of any required medical care also was examined. It was determined that a system similar to the "Integrated Medical and Behavioral Laboratory Measurement System (IMBLMS)" or the "Space Technology Applied to Rural Papago Health Care (STARPAHC)" would be appropriate for modification for use in space. Although these systems are not automated

in their present state, they contain many of the features necessary to perform a remote examination, deliver medical care, and operate a monitoring system.

By modifying microprocessor based clinical instrumentation which is currently available, the automated analysis of clinical and physiological data would be possible. The system would continuously monitor the status of the crew and independently separate research oriented data, then reduce and catalog it. The monitoring portion of the system would be used to detect abnormal responses from the crew. The detection of acutely occurring abnormal changes in the crew was also examined in this contract and was summarized in TIR 741-LSP-8012, "Statistical Design of Space-Flight Experiments." The identification of long-term abnormal changes and the problem of data base management was presented in TIR 741-LSP-9020, "Preliminary Study Requirements of Computerized Data Base and an Automatic Analysis of Human Clinical Data." Additionally, the research oriented system would be capable of statistical analysis and simulation studies using the crew data.

The future research principally should concentrate on the physiology of weightlessness and the development of models which can be used to simulate an integrated response of several organ systems when they are exposed to weightlessness. Such a model is the whole-body algorithm. Although the whole-body algorithm does attempt this, at present it does not function in real-time. Additionally, to improve access to the data base and to aid in analysis, a computer structure should be developed which allows parallel and essentially simultaneous use by the inflight and ground-based monitoring systems. The majority of the inflight systems should be dedicated to detection of abnormal function, while the ground system should concentrate on simulation, statistical analysis, and display of the data. Once a task is completed, the results could be displayed in either system.

2.6 (TASK 5.6) EXPERIMENT DESIGN, DEVELOPMENT, AND EVALUATION

The objective of this task was to use the systems analysis techniques, developed under the Skylab Medical Experiment Data Evaluation Program (SMEDEP, NAS9-14523), in conjunction with physiological research to aid some of the JSC Life Sciences investigators in directing their research programs. Of particular interest was the use of systems analysis to support the conception, design, and development of experiments. The feasibility of using systems analysis in such a manner was tested on the Spacelab proposals.

This task involved the following four subtasks:

- 1) provide a succinct description of hypotheses to be tested or evaluated;
- 2) provide pertinent information about the experiment, including how it could be applied to physiological questions of zero gravity;
- 3) provide suggestions for experiment design; and
- 4) develop technical requirements and specifications for the candidate experiments.

2.6.1 Development of Experimental Hypotheses

The purpose of the first subtask was to provide a brief description of the hypotheses suggested by the systems analysis that are to be tested or evaluated. Toward this end, the task monitor suggested that systems and hypotheses diagrams be used to present the physiological mechanisms in an unambiguous manner. Descriptions of hypotheses suggested for testing or evaluation were presented to the investigators of the musculoskeletal, cardiovascular, energy metabolism, and fluid and electrolyte areas.

2.6.2 Relationship of Experiments to Physiological Adaptation to Zero Gravity

The second subtask called for the contractor to supply previous findings and data pertinent to selected hypotheses or

experiments. The subtask also provided for discussion of the relationships between these experiments and the physiological questions of zero gravity.

2.6.3 Development of Experimental Design

The third subtask was concerned with experiment design. Design was to be based upon the results of previous related experiments, simulations of past related experiments, or simulations of the proposed experiment. To further assist NASA investigators in the experimental design, two statistical consultants (John Robinson and Steve Engle from General Electric Technical Support Systems Development Information Systems Programs) were retained. The consultants were provided with a set of requirements relevant to the design of the experiments in the Spacelab proposals. During their visit to Houston, the consultants worked with NASA investigators and members of the systems analysis team to refine the questions and present preliminary findings. The results of this effort were documented in TIR 741-LSP-8012, "Statistical Design of Space-Flight Experiments."

2.6.4 Development of Technical Requirements and Specifications for Experiments

The fourth subtask involved the development of technical requirements and specifications for the candidate experiments. The material in this subtask was prepared and delivered to the principal investigators in the musculoskeletal, cardiovascular, and fluid and electrolyte areas.

The systems analysis capability currently exists for five investigative areas: musculoskeletal, cardiovascular, energy metabolism, fluid and electrolyte, and hematology. The task monitors associated with the musculoskeletal, cardiovascular, and fluid and electrolyte areas used the inputs provided by the systems analysis in the preparation of their experiment proposals. The three proposals supported in this effort were "A Study of Bone Loss in Weightlessness" by Rambaut et al., 1979; "Fluid and

Electrolyte Regulation During Space Flight" by Leach et al., 1979;
and "Human Cardiovascular Adaptation to Space Flight" by Sawin, 1979.

3.0 SUMMARY AND CONCLUSION

The biomedical monitoring programs of NASA have been designed to support two objectives: (1) the development of a real-time system of data analysis and decision making to assure the greatest possible crew safety and mission success; and (2) the acquisition of information about man's abilities, limitations, and characteristic reactions to weightless space flight. This latter objective is essential to the planning of long duration manned space flight. The most important underlying goal of the Biomedical Systems Analysis Program funded under this contract and its preceding programs (Skylab Medical Data Evaluation Program, NAS9-14523 and Automated System for Integration and Display of Physiological Data, NAS9-12932) was to provide a systems analysis context which integrated the two broad objectives stated above.

It was recognized that the indices normally used to evaluate crew health must be re-evaluated in the light of known physiological adaptive effects in the weightless state. Earlier approaches for maintaining crew health were very comprehensive because of the many uncertainties of space flight. An alternative approach, explored here, was to identify those critical areas where physiological change is most likely to occur, and to develop methods for predicting these trends so that deviations from the norm can be estimated. Consequently, a definition of normal body function during zero-g adaptation was sought by a systematic examination of past flight data coupled with the development of a unified set of physiological hypotheses. This led to development of the capability to predict a normal zero-g physiological response, based upon simulations using quantitative models. Systems have been designed, using these models, to automatically predict deviation from the normal state by comparing fresh data with past data. Such an approach may offer both clinicians and physiologists a convenient manner in which to describe the real continuum from optimal health to overt pathology.

During the current contractual period, the heaviest emphasis was on interrelating the major biomedical space-flight findings through the formulation of a unified hypothesis for adaptation to

space flight. At the same time, analysis techniques were identified that could utilize this information for defining and monitoring in-flight physiological status. As in past programs, the Contractor continued the support of the experimental activities of principal investigators in several major disciplines. This latter effort involved: (a) developing the predictive capabilities of simulation models in the areas of fluid-electrolyte regulation, erythropoiesis regulation, and calcium regulation; (b) analyzing ground-based and space-flight data; and (c) assisting with the development of objectives, hypotheses, and design of experiments that would help clarify certain critical areas of space-flight adaptation.

This section contains a summary of the conclusions reached in each of the main areas covered by the present contract. For a discussion of more specific and detailed conclusions, the reader is referred to the complete documentation for this contract, listed in Appendix A.

3.1 CREW HEALTH MONITORING

A long-term objective of this project was the development of a health-care monitoring system for use in advanced mission programs. Such a system should consider engineering, operational, scientific, and human factors. At the very minimum, this system should involve: (a) establishing new standards for remote medical monitoring, diagnosis, and treatment; (b) evaluating crucial indices of health, fitness, and performance; (c) developing and testing instrumentation for measuring these parameters; and (d) designing and implementing sophisticated data acquisition and data analysis programs.

A more immediate objective was to define and develop procedures and systems to acquire and analyze the biomedical data necessary to establish man's ability to perform indefinitely during prolonged space missions at a high physical and mental level. Within this context, the following tasks were addressed during the current contract period: (a) a summary of the normal adaptive physiological processes which occur during space flight; (b) a definition of crew health in terms of these adaptive processes; (c) a state-of-the-art survey of remote health-care delivery system; (d) recommendations

for performance criteria based on static and dynamic physiological status during space flight; and (f) design requirements of information and processing subsystems as part of an overall biomedical monitoring data analysis system.

The work accomplished under this project has made it clear that an adequate health-care delivery system for remote space operation will require a broad-based scientific/engineering research program with a relatively long development time. The emphasis of both the current and previous contractual studies has been on understanding the physiological basis and the research requirements of such a system. In the past, there has been a more pressing need for the support of a biomedical space research program than there has been for actual hardware development. This was appropriate because of the great need to first understand the physiological basis of the changes brought about by space flight. In the future, the task of developing an advanced health care system should receive increasing priority. Preliminary studies indicate that much prototype hardware already exists in the health care arena, and since the software requirements can evolve from the present state of the systems analysis effort.

The need for a sophisticated system for the collection and integration of health-related data becomes more apparent when one considers the effect of an increase in mission duration, or the frequency of flight, as well as the fact that the population of future space travelers will be more varied and much larger than that which flew on past missions. It will be increasingly important to relate the activities of those responsible for crew health to those performing ground and flight research so that research results may be applied quickly to crew health. The entire systems analysis approach referred to in this report has evolved with this goal in mind.

3.2 INTEGRATION OF SPACE-FLIGHT FINDINGS

One project which received considerable attention during this contract was the preparation of the NASA Reference Publication An Integrated Analysis of the Physiological Effects of Space Flight.

This effort has served to unify the entire systems analysis approach whose results were obtained over a time period spanning the present and two previous contract periods. The reference publication will summarize the tools and techniques developed for space-flight data analysis and computer simulation of physiological processes. More importantly, it will address each major area which was examined (i.e. fluid-electrolyte regulation, cardiovascular regulation, hematology, and musculoskelton metabolism) by summarizing major findings, identifying critical areas, proposing hypotheses, and presenting experimental and theoretical evidence to test these hypotheses. Specific conclusions regarding each of these investigative areas will be presented in terms of homeostatic control theory. This approach, coupled with the validation of simulation models embodying hypotheses for adaptation to zero g, provides a firm physiological basis for developing the capability of predicting crew health status and a means of testing the efficacy of counter-measures under environmental and metabolic conditions different from those found on previous flights.

The approach used in this part of the biomedical systems analysis project was successful in that it satisfied the basic program objectives. However, this does not imply that the approach had provided a definitive theory of the physiological effects of space flight. Rather, what was done was to examine available evidence to support or deny various scientific hypotheses, identify qualitative and quantitative interactions between various experimentally measured responses to space flight, and propose a tentative integrated physiological hypothesis for the adaptive processes in weightlessness. Perhaps of equal importance, the approach taken to this problem has served to organize the observed effects of space flight and to compare them to a collection of published theories representing current knowledge of the physiological systems involved. This approach raised many questions which, in turn, suggested some of the next logical objectives for future space-flight experimentation.

3.3 PHYSIOLOGICAL SYSTEMS ANALYSIS

Physiological systems analysis was carried out in three major disciplines; erythropoiesis regulation, fluid-electrolyte regulation, and musculoskeletal metabolism calcium regulation. The major conclusions resulting from this work are presented below.

3.3.1 Erythropoiesis Regulation

The systems analysis of erythropoiesis regulation has contributed significantly to the understanding of the mechanisms potentially responsible for red blood cell mass lost during space flight. The computer model demonstrated the erythrocyte-producing mechanisms have high sensitivity to tissue oxygenation, particularly to small changes in plasma hemoglobin concentration. Inasmuch as hemoconcentration appears to be an invariable consequence of space flight, this hyperoxia-inducing pathway was a likely candidate to account for suppression of erythropoiesis and the gradual depletion of red blood cell mass. The model simulations suggested that loss of red blood cell mass is self-limiting, since hemoglobin concentrations tend to normalize as red blood cell mass diminishes. Animal studies, which were supported by the system analysis effort, further demonstrated that a negative energy balance resulting from dietary restriction can play a role in suppressing red blood cell production also, perhaps by a direct effect on the bone marrow. An energy balance analysis of the Skylab crew provided evidence of negative energy balance, especially early in flight. Therefore, hemoconcentration and negative energy balance, at present, appear to offer the most plausible explanation of red blood cell mass decrements during prolonged space flight. There was also some indication of hemolysis on one flight that could explain the larger cell losses in those crewmembers. The originally proposed theory that red cell mass regenerated in flight was examined, and it remains viable, although sufficient data is not available (and will not become available in the near future) to test its veracity. However, it is not necessary to invoke the occurrence of red cell regeneration to explain the available data.

Among the various ground-based maneuvers available to simulate the hematological effects of space flight, bed rest remains the most valuable for human subjects. Mice dehydration studies, examined in simulation as well, provide the opportunity to study short-term effects of relative erythrocytosis. However, this experimental technique does not lend itself to longer term studies, and it is confounded by an associated negative energy balance. Thus, the computer model is an extremely valuable tool for simulating zero-g effects on erythropoiesis and it provides a strong, common link between diverse experimental studies, whether on the ground or in space.

3.3.2 Fluid-Electrolyte Regulation

During Skylab, a large volume of data related to the fluid-electrolyte regulating systems was collected. This quantity of information, in contrast to the more limited data base related to erythropoiesis regulation, necessitated a concurrent program of data analysis and simulation studies. The foundations and techniques for these tasks were developed under previous contracts; during the current contractual period these tasks were carried to a logical conclusion.

In the area of data analysis, the major achievement was the formulation of an integrated metabolic balance analysis, resulting in a quantitative answer to the question "how and why do astronauts lose body weight during space flight?". A unique numerical analysis method was developed to determine continuous time profiles which showed the changes in body water, body protein, and body fat. Differences between the different crews could be correlated with the degrees of motion sickness encountered, the levels of exercise performed, and the amounts of food consumed. This information should prove valuable in predicting dietary and exercise levels on future missions and in establishing predictions for obligatory weight losses for crewmembers of different physical condition and body composition. The body composition analysis complements the analyses of water, electrolyte, and energy balance previously performed, and provides a basis for validating the fluid-electrolyte simulation model for

zero-g hypotheses. An additional data-analysis task was the formulation of "nine-man averages" for the major renal, electrolyte, and endocrine losses. These averages presented the data in a more statistically meaningful manner and thus provided a more comprehensive picture of the fluid-electrolyte space-flight response than was previously available.

Simulation studies focused on integrating the short-term and long-term responses to hypogravity. It is during the acute period (the first 48 hours) that most dramatic changes appear to occur, but space-flight data from this time-frame is sparse. Simulation studies provided not only plausible explanations of the events during this period, but also made it possible to demonstrate how the longer term responses develop from these changes. One of the achievements of the systems analysis study was to define some of the mechanisms potentially operative during the short-term, acute segments of flight, but which are less important during the longer term, adaptive state. Mechanisms which adapt to chronic disturbances (such as reduced blood volume) assume importance as a function of time spent in space, according to model behavior, but these processes are experimentally not well defined. Computer simulation has provided a technique to easily test hypotheses about the adaptive period of space flight. Modifications made to the existing fluid-electrolyte model permitted realistic simulations of water immersion and head-down bed rest.

The comprehensive nature of the fluid-electrolyte system analysis will be demonstrated in the NASA reference publication. Studies done during the past three contractual periods will be combined and summarized by category in this document. These categories include: (1) integrated metabolic balance analysis (water-electrolyte-energy balances and body composition changes); (2) major Skylab fluid-electrolyte-endocrine findings; (3) systems analysis of body fluid regulation, hypotheses, and supportive simulation studies to account for the major findings; and (4) integrative simulation analysis of fluid and electrolyte disturbances during gravity alterations (i.e. postural change, water immersion, supine bed rest, head-down

bed rest, and space flight). These results, when taken as a whole, support the contention that a careful analysis of fluid shifts and disturbances is essential before the various physiological systems' responses to zero g can be understood. The changes in hydrostatic gradient which initiate the fluid shifts were found to be perhaps the most important factor influencing the initial loss of water and salts. However, the extent of musculoskeletal tissue atrophy which is seen as a result of the changes in gradient is also crucial to understanding the effects of longer term exposure to zero g. Furthermore, both food intake and metabolism decrease in bed rest while food intake appears to decrease in space flight. This diminished food intake certainly modifies the body's early response to headward fluid shifts and this factor helps to obscure any diuresis response. All of these events have both acute and long-term effects on the major physiological systems, resulting in weight loss and decreased tolerance for orthostasis and work.

3.3.3 Musculoskeletal Metabolism/Calcium Regulation

Musculoskeletal metabolism and calcium regulation were new areas for systems analysis investigation. Consequently, systems analysis techniques for use in these areas were not fully developed when this contractual period began. Nevertheless, systems analysis of these two areas yielded useful conclusions in terms of hypothesis development. Systems analysis made even greater contributions to the design and development of a simulation model and data base. The major tasks related to the musculoskeletal system were: (1) summarizing the biomedical findings of space flight and bed rest studies; (2) defining the calcium metabolic and regulatory pathways; (3) designing a simulation model; (4) assembling a data base and analysis system for future validation studies; and (5) analyzing the effects of muscle atrophy seen during flight.

A summary of the Skylab data and an understanding of the calcium metabolic and regulatory pathways led to the design and partial development of a calcium simulation model. The major routes of calcium gain and loss appear to be the intestinal tract (by absorption or lack of absorption), the kidney, and the bone. When this

model is complete, its major regulatory mechanisms will be parathyroid hormone, calcitonin, and the metabolites of vitamin D. Regulatory mechanisms associated with mechanical stresses are thought to be important to bone maintenance. However, there appear to be insufficient data describing mechanical stresses and related skeletal calcium fluxes. Consequently, the effects of these stresses probably will not be included in the initial model. The major problem anticipated with the model is the representation of the bone. However, the model is expected to have a good representation of the soft tissues, especially the kidney and intestinal tract. If the soft tissue subsystems provide adequate simulations of the real system, preliminary hypotheses concerning vitamin D and kidney excretion can be tested, as well as preliminary hypotheses addressing the role of bone.

Space-flight data regarding calcium losses and muscle atrophy were analyzed and interpreted. The major conclusions are briefly described below:

(1) Calcium Loss: The results collected from the Skylab crews suggested that the integrity of particular bones began to decay when exposed to space flight. The densitometric data shows a less dense calcaneus after exposure to zero g. These data were supported by negative calcium balances and increased excretion rates of hydroxyproline and hydroxylysine. Most of these analyses showed negligible losses after the first month inflight. All of the analyses showed increased losses the second month, and some of them showed progressive losses that could be related to flight duration. The skeletal losses are assumed to be related to the lack of mechanical stresses in the zero-g environment, although their exact nature is unknown. However, it is known that there is slight increase in plasma calcium and or increase in the urinary excretion of calcium. There is also a progressive increase in fecal calcium, suggesting a decrease in the absorption of dietary calcium. The nature of the kidney excretion has not been determined, but the reduced intestinal absorption has been hypothesized to result from a decrease in plasma 1,25 dihydroxycholecalciferol.

(2) Muscle Atrophy: The body composition analysis resulted in quantitative assessment of the dynamics and degree of muscle atrophy occurring during space flight. The most important conclusions drawn from this analysis were: a) protein losses are initiated almost immediately after entering weightlessness; b) loss rates decrease exponentially with time during the first month; c) after the first month of flight, protein losses stabilize; and d) these losses occur in spite of a high protein diet and exercise training. All of these findings are consistent with the hypothesis that the postural muscles are virtually unused in weightlessness and therefore atrophy from disuse. A variety of inflight and postflight measurements were considered in this assessment. Ground-based studies of muscle atrophy in immobilized animals were also reviewed and these studies supported these conclusions. In addition, recent studies in identification of muscle-loss mechanisms through the use of iso-enzyme analysis were reviewed for applicability to onboard experiments

3.4 SUPPORT OF NEW EXPERIMENTAL PROGRAMS

In addition to analysis of previous experimental studies, this contract period was characterized by a shift of emphasis toward support of new areas of experimental research. Based on the experience developed in the systematic analysis of space-flight biomedical studies, the Contractor provided support in proposing and designing experiments for inclusion in the Shuttle Spacelab. Contributions were directed toward three major investigative areas: fluid-electrolyte metabolism, cardiopulmonary function, and calcium regulation. A proposal also was submitted to the joint US/USSR bed rest study team. This proposal included specific suggestions for data collection and processing, as well as methods for predicting physiological trends using simulation models. An additional task that proved fruitful was the undertaking of animal studies which were designed to elucidate erythropoiesis regulation during hypogravic exposure. This latter study, in particular, demonstrated the utility of simulation modeling when it is used in an iterative manner, and in conjunction with an active research program. All of the experimental

programs cited above are central to NASA's interdisciplinary effort in support of basic physiological research and crew medical safety.

A new area of research support was initiated during this contractual period in the form of statistical design requirements for space-flight experiments. A statistical approach was developed that considered the special operational constraints of Spacelab experiments (i.e. limited number of subjects and replicate measurements) and established guidelines for determining confidence limits of expected results. The full potential of this approach has yet to be realized, but it is expected to be widely applicable to the evaluation of Spacelab experiments.

In addition to its value as a research tool, systems analysis has also proved valuable in science management for coordinating biomedical research programs. The principal investigators were provided descriptive flow-chart diagrams of each physiological system. All of the important elements of the system as well as the feedback nature of their interrelationships from these flow-chart diagrams could be easily discerned. Critical areas requiring greater experimental emphasis were identified on the diagrams, and the research projects supported by the NASA scientific programs in each discipline were placed into proper physiological perspective. These diagrams proved to be good communicative devices and were used in management reviews by several of the task monitors.

4.0 RECOMMENDATIONS

The fundamental contribution of the systems analysis effort supported under this contract has been to organize many of the major biomedical findings from space flight and correlate these findings with the scientific theories that describe the requisite organ systems. Out of this effort has come two kinds of end-products. One of these is an array of methods, tools, and techniques that has proven essential for the handling, processing, and interpreting of experimental data in general, and space-flight data in particular. The other result is an improved understanding of the physiological events which occur during human adaptation to weightlessness and the concomitant identification of critical areas ripe for future study. Most recommendations offered will be derived from and directed toward future development in one of these two areas.

The present program was undertaken and completed in the lull between two major NASA programs - that of Skylab and that of Shuttle. The experience and expertise which were gained in the analysis of the biomedical results of Skylab do have direct applicability to the Shuttle program. The Shuttle missions, with their proposed frequent flights and large number of crewmembers will require substantially greater effort in both the areas of crew health monitoring and scientific support of biomedical research. The systems analysis program has already demonstrated its utility in each of these areas. Therefore, the strongest recommendation that will be made is that the present systems analysis program be renewed and directed toward supporting the Shuttle program in the areas pertaining to crew health and physiological research.

The rest of this section will be devoted to making a large number of general and specific recommendations concerning future work. These recommendations are divided into those that concern physiological analyses, and those that concern other, more general, systems analysis work.

4.1 RECOMMENDATIONS FOR PHYSIOLOGICAL RESEARCH

These recommendations concern proposals for new experiments which would clarify "soft" areas, provide missing information, test

hypotheses, and provide data for validation models. The physiological systems analyses, computer model studies, and space-flight data analyses conducted during the course of this contract form the basis for these suggestions. For convenience they have been categorized according to investigative area.

4.1.1 Hematology/Erythropoiesis

1. The most pressing problem in this area is to understand the nature of the loss of red cell mass during space flight. The most serious data limitation is lack of direct measurements of red cell mass, plasma volume, plasma erythropoietin, and erythropoiesis rate during flight. It is important to ascertain if hemolysis occurs early in flight, if erythropoietin levels decline, and if red cell mass regenerates in flight. Regeneration studies would require missions longer than one month.
2. Secondary information is required regarding tissue oxygenation during relative polycythemia, both in space and on earth. Direct measures of tissue pO_2 , blood $p50$, and renal plasma flow would be useful in this regard. Kinetics of stem-cell proliferation needs to be examined by studying changes in size, density and sensitivity of marrow cultures.
3. Skylab data suggest a diminished red-cell loss with increasing exercise and diet. However, adequate controls were lacking in previous work. The effects of exercise and diet on erythropoiesis need to be studied more thoroughly.
4. The two most likely theories accounting for red cell loss, hemoconcentration and negative energy balance, need to be fully examined under space-flight conditions.

4.1.2. Fluid-Electrolyte Regulation

1. The most pressing need in this area is to measure circulatory, fluid, and electrolyte disturbances, and associated endocrine alterations during the first 24-48 hours of flight. Experiments should be directed at confirming the mechanisms of body water/plasma volume reductions suggested by the unified hypothesis developed during the present contract. Alternative explanations

to account for the lack of observed diuresis are dehydration, insufficient urine collection, effect of motion sickness and drugs, and stress. It is therefore important to ensure that subjects are adequately hydrated, that urine is collected on a void-by-void basis, that data is collected sufficiently early after launch, and that adequate control studies are included.

2. In light of the above discussion, the following specific measurements are suggested;
 - a. indices of renal function including excretion rates (void-by-void), renal clearances, glomerular filtration rate, and renal blood flow;
 - b. body fluid volumes including plasma and extracellular fluids and total body water;
 - c. leg volumes and central blood pressure;
 - d. electrolytes, protein, and hormone levels in plasma and urine.
3. Many of the pathways suggested to explain fluid and electrolyte regulation during space flight need more detailed examination than can be performed in space flight. Some objectives can be suggested for ground-based studies, including;
 - a. verifying the effects of exercise, diet, and motion sickness on fluid-electrolyte and musculoskeletal responses;
 - b. studying the alternative pathways for plasma volume regulation consisting of renal excretion, transcapillary exchange, and drinking;
 - c. determining the contribution of a natriuretic factor in producing hyponatremia and in opposing aldosterone's effect on sodium excretion;
 - d. determining the origin of fluids which disappear from the legs (i.e. blood, interstitial, intracellular) and determining the eventual distribution of this fluid in other regions of the body;
 - e. identifying the longer term adaptive mechanisms that are involved in circulatory and renal adaptation to prolonged hypogravity.

4.1.3 Cardiovascular Regulation

1. The most immediate effects of space flight probably originate in the cardiovascular system. A combination of hemodynamic, neural, and endocrine mechanisms are involved in the response to headward fluid shifts but the extent of their participation and their time course are not known. The ultimate reduction in blood volume produces some long-term effects that are also not well understood but manifest themselves in potentially harmful ways upon return to earth's gravity. Both acute and long-term cardiovascular regulation require additional study.
2. Several aspects of the headward fluid shift phenomena need to be examined in more detail, including: a) the magnitude and duration of the original fluid volume shift; b) its origin in the fluid compartments of the legs (i.e. intravascular versus extravascular, interstitial versus intracellular); c) degree of long-term fluid storage in upper body following major adjustment and reduction of body fluid volume; d) changes in venous pressure and possible development of pulmonary hypertension; e) possible adaptation of the volume receptors in the face of prolonged upper body congestion.
3. Experiments should be designed specifically to examine the involvement of the circulatory pressure receptors in both the long-term adaptive response and in periodic acute stresses such as LBNP and exercise. Experiments should be constructed to selectively distinguish between high and low pressure receptors and to observe adaptive effects such as changes in sensitivity and gain.
4. Clarifying experiments related to cardiovascular instability upon return to gravitational influences are needed. This includes developing an understanding of the basic mechanisms involved in the response to hypovolemia as observed during such stresses as tilt, LBNP, hemorrhage , and in hypotension. An understanding of venous regulation (compliance, resistance, volume) and autonomic regulation are especially important.

5. The relationship of the cardiovascular system to the regulator systems for blood volume, body fluid composition, and endocrine-renal function needs to be examined. These relationships have been hypothesized in detail during the course of the systems analysis project but need experimental verification.
6. There is a critical need for more information regarding exercise as a countermeasure for deconditioning during space flight. The definition of deconditioning should be extended to include all effects which are deleterious upon return to earth and include effects on autonomics, muscle, bone, and circulatory volume and capacity.

4.1.4 Musculoskeletal Metabolism/Calcium Regulation

1. A more intensive program for studying muscle atrophy is required. Experiments should be directed at determining mechanisms, effect of diet and exercise, loss rates, and iso-enzyme characteristics of tissue samples.
2. It is necessary to develop more precise and accurate methods to determine bone mass and mineral content, including a method applicable for inflight use. Interpretation of present flight data suffers from lack of measurement accuracy and from the small number of subjects studied.
3. Plausible hypotheses for bone atrophy during space flight require detailed study. Possible mechanisms involve the absence of direct physical stress, diminished muscle tension on the periosteum, circulatory changes, and hormonal changes.
4. An experimental program should be developed for validating critical portions of the mathematical model of calcium regulation, including the areas of: gastro-intestinal absorption, vitamin-D metabolism and its effects, parathyroid and calcitonin regulation, and renal handling.

4.2 RECOMMENDATIONS FOR SYSTEMS ANALYSIS RESEARCH

4.2.1 General Analysis

1. Continue the systems analysis support of in-house research in the following areas: fluid-electrolyte metabolism/renal function.

hematology/erythropoiesis, musculoskeletal metabolism/calcium regulation, and cardiovascular regulation. It is suggested that vestibular function/space motion sickness be added as a new investigative area for systems analysis support.

2. Continue the use of systems analysis to provide the means to unify results from the different disciplinary investigative areas cited above.
3. Use results embodied in the NASA reference publication An Integrative Analysis of the Physiological Effects of Space Flight (in preparation) to help define objectives for research and to assist in the evaluation of experimental proposals, particularly with regard to Spacelab.
4. Use the general systems analysis approach to provide coherence to all the proposed Spacelab experiments in any one investigative discipline. This function should include: insuring adequate coverage of critical measurements, verifying requirements for simultaneous measurements and replicate measurements, designing proper statistical support, combining several experiments into one package, developing a common data base for the handling, analysis, and documentation of experimental results.
5. Develop a common data base and data processing system for organizing, processing, and integrating baseline and inflight crew biomedical data. The purpose of this system would be to support both crew health monitoring programs and experimental programs. The system would be modeled after existing space-flight data bases and would be a prototype subsystem for an advanced crew health monitoring system.
6. Perform comparative analyses of space flight and its ground-based analogs, bed rest (supine and head-down), and water immersion. The systems analysis techniques of both data and simulation analysis would be ideal for such a study. The following areas should be examined: musculoskeletal function, fluid-electrolyte regulation, cardiovascular status, body-composition changes, effects of dehydration, effects of diet, effects of exercise, effects of drugs, effects of countermeasures.

7. Continue development of model capabilities for obtaining non-invasive measurements on difficult to measure quantities.
8. Continue development of performance criteria for indexing physiological status in specific investigative areas.
9. Continue development of sensitivity and error analysis, and combine these with statistical models to determine accuracy requirements in experimental measurements.
10. Transfer programs and data base from UNIVAC to VAX computer system. This will increase available core size, improve efficiency of operation, and consolidate data base and simulation models.

4.2.2 Hematology/Erythropoiesis

1. Areas identified for future improvements in the erythropoiesis control model include:
 - a. a more realistic description of erythrocyte production, including stem cell proliferation and kinetics, more realistic transit delays, variable sensitivity to erythropoietin levels, and reticulocyte production;
 - b. a quantitative description of the effects of blood volume and viscosity on oxygen transport;
 - c. a new species specific model for the squirrel monkey to support current animal experiments;
 - d. a determination of the need for developing ferrokinetic models to support iron uptake studies;
 - e. the continued development of a teaching model for hematological abnormalities.
2. Recommendations for additional simulation studies include:
 - a. comparative sensitivity studies between models of human, mouse, and monkey system;
 - b. comparative studies between space flight and bed rest;
 - c. simulations of squirrel monkey experiments designed to mimic headward shifts using positive pressure leg garments.

4.2.3. Fluid-Electrolyte Regulation

1. Areas identified for future model improvements include:
 - a. construction of an advanced renal subsystem model including

peritubular capillary effects, third factor effects, and role of angiotensin on renal blood flow;

- b. re-evaluation of the ADH subsystem in light of new experimental findings;
 - c. determination of the feasibility of adding the renal excretion of hormone to existing models so that hormone concentrations can be predicted in both plasma and urine;
 - d. addition of an acid-base regulatory subsystem to the Guyton model.
2. Develop a unified collaborative program for supporting water immersion and bed rest investigations with systems analysis and computer simulation studies.

4.2.4. Cardiovascular Regulation

- 1. Use simulation models of the cardiovascular subsystem to organize various data related to cardiovascular stability during hypovolemia (e.g. LBNP, tilt, hemorrhage, hypotension, space flight, bed rest).
- 2. Develop a new autonomic subsystem which separates sympathetic and parasympathetic effects for inclusion in simulation models containing cardiovascular control.
- 3. Increase the level of support of systems analysis connected with the in-house cardiovascular research program.

4.2.5. Musculoskeletal/Calcium Regulation

- 1. Continue the development of a mathematical model of calcium regulation. This model should be operational within the next year, given the present level of effort. It should be valuable in integrating calcium/bone data, identifying critical areas, interpreting experimental results, and predicting trends under unusual circumstances.
- 2. Analyze the bed rest data assembled during current contract period. These data should be useful in the validation of the calcium model.

4.2.6. Crew Health Monitoring

- 1. Continue work on questions related to formulating a definition of crew health and identify the critical measurements required

for health evaluation.

2. Design a system for automated diagnosis of illness.
3. Develop simulation analysis capability for evaluating counter-measures for cardiovascular deconditioning, hypovolemia, reduced red cell mass, reduced orthostatic tolerance, muscle atrophy, and bone atrophy.
4. Develop a computer structure that permits parallel access to the data base and parallel processing. Inflight tasks will primarily be concentrated on detection of abnormal function and monitoring, while parallel ground-based tasks will concentrate on research, statistical analysis, cataloging, and display function.
5. Continue design and development of an automated crew health monitoring system, incorporating, if possible, existing data and results from other flight and ground-based clinical (intensive care) programs.
6. Use a systems analysis approach to relate the activities of those responsible for crew health to those performing research so that research results may be quickly applied to crew health.

4.2.7. New Projects

1. Study feasibility for the development of mathematical models of vestibular function. Develop collaboration with in-house vestibular investigators.
2. Organize a conference/workshop on application of simulation models to space biomedical problems. This type of conference has not existed previously and NASA is the only plausible agency for sponsoring such a program.
3. Perform a feasibility study exploring the development of models of closed ecological life support systems. These models will require consideration of biological components, such as the food chain, as well as physical and chemical processes for water reclamation, and waste contaminant control. This type of system lends itself well to the rigors of mathematical modeling and can contribute substantially to a total research program. A model of advanced life support systems can be combined with models of physiological function for a total man-environment model.

Simulation studies would provide a rapid, inexpensive method of testing new system design as well as the long-term effects of life support systems under unusual environmental and metabolic conditions.

4. Apply the systems analysis approach to the overall management problems of the NASA Life Sciences Program. This approach has the capability of contributing to management skill in a fundamental manner.

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APPENDIX A
COMPLETE DOCUMENTATION COMPRISING FINAL REPORT
Tasks in Original Statement of Work and Documentation
Associated with Each

- 5.1 DEFINITION OF ADVANCED HEALTH MONITORING TECHNIQUES
 - 5.1.1 State of the Art Survey of Automated Health Monitoring Systems
TIR 741-LSP-9022
 - 5.1.2 Candidate List of Physiological Parameters
TIR 741-LSP-8033
 - 5.1.3 Sensitivity of Measured Physiological Parameters
TIR 741-LSP-8012
TIR 741-LSP-9005
Appendix F of NASA reference publication (now in preparation)
Presentation by J.I. Leonard, et al., 1979 (a)
 - 5.1.4 Modeling Approaches for Predicting Physiological Indices of Health
TIR 741-LSP-8023
TIR 741-LSP-9016
TIR 741-LSP-9023
Presentation by J.I. Leonard et al., 1979 (b)
 - 5.1.5 Physiological Criteria for Zero-g Health
NASA reference publication (now in preparation)
 - 5.1.6 Transfer of Programs and Data Bases from the Univac 1110 to the DEC
Completion report in the Quarterly Report, TIR 741-LSP-8025
- 5.2 COMPUTER SIMULATION OF THE EXISTING ERYTHROPOIESIS MODEL
 - 5.2.1 Application of the Existing Erythropoiesis Model
TIR 741-LSP-8004
TIR 741-LSP-8029
TIR 741-LSP-9005
Presentation by J.I. Leonard et al., 1979 (a)
Publication by Kimzey et al., 1979

5.2.1 (con't.)

Leonard, J.I., and C.D.R. Dunn, 1979, submitted to Blood
Leonard, J.I., 1979, submitted to Aviation, Space, and Medicine.

5.2.2 Feasibility Study for Developing a Species Specific Model of Erythropoiesis

TIR 741-LSP-8024
TIR 741-LSP-8029
TIR 741-LSP-9002
Presentation by J.I. Leonard et al., 1979 (a)
Transfer of Model to University of Tennessee

5.2.3 Improvement to Erythropoiesis Control Model

TIR 741-LSP-9004
TIR 741-LSP-9016
TIR 741-LSP-8004
TIR 741-LSP-8024
Presentation by J.I. Leonard et al., 1979 (a)

5.2.4 Development of a Teaching Model from the Current Model of Erythropoiesis

TIR 741-LSP-9023

5.2.5 Systems Analysis to Define Interrelationships Between Selected Zero-g Observations

NASA reference publication (now in preparation)

5.3 DEFINITION OF CHANGE AND CONTROL MECHANISMS IN FLUID ELECTROLYTE METABOLISM5.3.1 Simulation of Short-Term Response to Weightlessness

TIR 741-LSP-8023
Presentation by Leach et al., 1979
NASA reference publication (now in preparation)

5.3.2 Model Simulations Implemented

TIR 741-LSP-9017
TIR 741-LSP-9021
Presentation by Leonard et al., 1979 (b)
Presentation by Leach et al., 1979
NASA reference publication (now in preparation)
Presentation by Leonard et al., 1978.

5.4 INTEGRATED ANALYSIS OF MUSCULOSKELETAL CHANGES

5.4.1 Overall Systems Analysis of Physiological Regulation

TIR 741-LSP-8009

TIR 741-LSP-8010

TIR 741-LSP-8011

TIR 741-LSP-9004

TIR 741-LSP-9024

TIR 741-LSP-8015

TIR 741-LSP-8022

NASA reference publication (now in preparation)

Presentation by S.N. Brand, 1979

Presentation by D.J. Grounds, 1979

5.4.2 Space-Flight Data Analysis and Integration

TIR 741-LSP-8015

TIR 741-LSP-9019

NASA reference publication (now in preparation)

Bed Rest Data Transferred from San Francisco to JSC

5.4.3 Integration of Bed Rest Data and Space-Flight Data

TIR 741-LSP-8012

NASA reference publication (now in preparation)

5.5 MODEL AND DATA ANALYSIS SYSTEMS REQUIREMENTS

TIR 741-LSP-9022

TIR 741-LSP-9020

5.6 EXPERIMENT DESIGN, DEVELOPMENT, AND EVALUATION

TIR 741-LSP-8012

TIR 741-LSP-9020

Flight Experiments Proposal Support for Fluid-Electrolyte,
Cardiopulmonary, and Calcium Metabolism

NASA reference publication (now in preparation)

APPENDIX B
Outline for NASA Reference Publication
An Integrated Analysis of the Physiological Effects
of Space Flight

- Section I Executive Summary
- Section II Introduction
- Section III Approach and Analytical Techniques
- Section IV A. Team Concept
- B. Data Base and Analysis System
- C. Description of Simulation Models
 - 1. General Model Descriptions
 - a. Stages of Model Development
 - b. Validation
 - 2. Cardiovascular Model
 - 3. Thermoregulatory Model
 - 4. Respiratory Model
 - 5. Red Blood Cell Model (Erythropoiesis Model)
 - 6. Circulatory, Fluid and Electrolyte Model
 - 7. Whole-Body Algorithm
 - 8. Calcium Model
- D. Hypothesis Testing Approach
 - 1. Preparation of Crew Data
 - 2. Hypothesis Testing and Development
- Section IV Integrated Metabolic Balance Analysis
 - A. Skylab Evaporative Water Loss Analysis
 - B. Skylab Water Balance Analysis
 - C. Skylab Na and K Balance
 - D. Integration of Fluid and Electrolyte Balance
 - E. Quantification of Tissue Loss Resulting from Prolonged Space Flight
 - F. Energy Balance and Composition of Weight Loss During Prolonged Space Flight

APPENDIX B (Continued)

- Section V Subsystem Hypothesis Development and Evaluation
 - A. Fluid and Electrolyte Regulation
 - B. Hematology
 - C. Cardiovascular
 - D. Calcium and Musculoskeletal System
- Section VI Integrated Systems Analysis
 - A. Simulations of Bed Rest Without Legs
 - B. Simulations of Bed Rest With Legs
 - 1) Postural Changes
 - 2) Bed Rest
 - 3) Head-Down Tilt
- Section VII Discussions and Conclusions
- Section VIII Potential for the Future
- Appendix A: Modeling and Simulations of Feedback Control System
 - B: Detailed Red Blood Cell Model (Erythropoiesis)
 - C: Detailed Fluid and Electrolyte Model
 - D: Whole-Body Algorithm Model
 - E: Sensitivity Analysis and Its Application to Thermoregulation
 - F: Integrated Metabolic Balances: Methods of Computation and Assumptions, Error Analyses, and Supplementary Data

APPENDIX C

Presented or Published Scientific Papers
Related to ContractPRESENTATIONS

Brand, S.N. and D.J. Grounds: "Mathematical Model of Parathyroid Gland." 32nd meeting of the Alliance for Engineering, Medicine, and Biology, Denver, CO., 1979.

Grounds, D.J. and S.N. Brand: "Mathematical Model of Vitamin D Metabolism." 32nd meeting of the Alliance for Engineering, Medicine, and Biology, Denver, CO., 1979.

Leonard, J.I., D.J. Grounds, C.S. Leach, J.A. Rummel, P.C. Rambaut, and D.G. Fitzjerrell: "Simulation of Fluid and Electrolyte Responses During Space Flight." 31st meeting of the Alliance for Engineering, Medicine, and Biology, Atlanta, GA., 1978.

Leach, C.S., J.I. Leonard, and P.C. Rambaut: "Dynamics of Weight Loss During Prolonged Space Flight." American Physiological Society, New Orleans, LA., 1979.

Leonard, J.I., C.D.R. Dunn, and S.L. Kimzey: "Computer Simulation in a Potential Animal Model for Space Flight." Aerospace Medical Association, Washington, D.C., 1979 (a).

Leonard, J.I., C.S. Leach, and J.A. Rummel: "Computer Simulations of Postural Change, Water Immersion, and Bed Rest: An Integrated Approach for Understanding the Space-flight Response." American Physiological Society, New Orleans, LA., 1979 (b).

Leonard, J.I.: "Overview of Space-flight Modeling Applications." National Computer Conference, New York, N.Y., 1979.

Leonard, J.I.: "Erythropoiesis Regulation During Zero-g, Using Computer Simulation." Presented at University of Tennessee Memorial Research Center, Knoxville, TE., 1978.

PUBLICATIONS

Dunn, C.D.R. and S.L. Kimzey: "Interaction of Animal and Computer Models in Investigation of the Anemia of Space Flight." Submitted to Aviation, Space, and Environmental Medicine, 1979.

Kimzey, S.L., J.I. Leonard, and P.C. Johnson: "A Mathematical and Experimental Simulation of the Hematological Response to Weightlessness." Acta Astronautica, Vol. 6, pp. 1289-1303, Pergamon Press, Ltd., 1979.

APPENDIX D
Complete List of Technical Reports Associated
With This Contract

<u>TIR No.</u>	<u>Date</u>	<u>Title and Author</u>
741-LSP-8001	2/10/78	Program Plan for the Biomedical Systems Analysis Program - D. G. Fitzjerrell
741-LSP-8004	3/13/78	User's Instructions for the Erythropoiesis Regulatory Model - D. J. Grounds
741-LSP-8006	4/3/78	Quarterly Progress Report for Biomedical Systems Analysis Program - D.G. Fitzjerrell
741-LSP-8009	7/10/78	Study Report on: A Double Isotope Method of Calcium Absorption - S. N. Brand
741-LSP-8010	7/10/78	Study Report on: Strontium Metabolism in the Rebuilding of Skeletal Tissue - S. N. Brand
741-LSP-8011	7/10/78	Study Report on: The Influence of Exercise on Bone Atrophy - S. N. Brand
741-LSP-8012	7/17/78	Statistical Design of Space-flight Experiments- S. Engle and J. Robinson
741-LSP-8014	7/14/78	Simplified User Instructions for Physiological Models Using the Univac 1110 in Demand Mode - V. J. Marks
741-LSP-8015	7/17/78	A Brief Review of Space-flight Calcium Metabolism: Results and Methodologies - S. N. Brand
741-LSP-8016	7/14/78	Quarterly Progress Report for Biomedical Systems Analysis Program - D. G. Fitzjerrell
741-LSP-8022	10/6/78	Preliminary Design Specifications of a Calcium Model - S. N. Brand
741-LSP-8023	10/16/78	Study Report on Development of an Hypothesis for Simulating Anti-orthostatic Bed Rest - J. Leonard
741-LSP-8024	10/16/78	System Parameters for Erythropoiesis Control Model: Comparison of Normal Values in Human and Mouse Model - J. I. Leonard
741-LSP-8025	10/11/78	Quarterly Progress Report for Biomedical Systems Analysis Program for period 7-1-78 to 9-30-78 - D. G. Fitzjerrell

APPENDIX D (Continued)

<u>TIR No.</u>	<u>Date</u>	<u>Title and Author</u>
741-LSP-8029	11/7/78	Research Report: Use of a Computer Model in the Understanding of Erythropoietic Control Mechanisms - J. I. Leonard
741-LSP-8033	11/27/78	Study Report: A Prioritized Set of Physiological Measurements for Future Space-flight Experiments - D. J. Grounds
741-LSP-8034	11/29/78	Simplified User Instructions for Physiological Models Using the Univac 1110 in Demand Mode - V. J. Marks
741-LSP-9002	1/9/79	Quarterly Progress Report for the Biomedical Systems Analysis Program for the Period October 1, 1978 - December 31, 1978 - D. G. Fitzjerrell
741-LSP-9004	1/26/79	Study Report - The Role of Calcitonin in Calcium and Bone Metabolism - S. N. Brand
741-LSP-9005	2/2/79	Dynamic Regulation of Erythropoiesis: A Computer Model of General Applicability - J. I. Leonard
741-LSP-9009	4/9/79	Quarterly Progress Report for the Biomedical Systems Analysis Program for the Period January 1, 1979 - March 31, 1979 - D. J. Grounds
741-LSP-9015	7/9/79	Quarterly Progress Report for the Biomedical Systems Analysis Program for the Period April 1, 1979 - June 30, 1979 - R. E. Creamer
741-LSP-9016	7/25/79	Numerical Methods for Systems of Stiff Differential Equations: The Hybrid Euler Integration Technique - D. J. Grounds
741-LSP-9017	9/15/79	Quantitation of Tissue Loss During Prolonged Space Flight - J. I. Leonard
741-LSP-9018	10/12/79	Quarterly Progress Report for Biomedical Systems Analysis Program for the Period July 1, 1979 - September 30, 1979 - J. I. Leonard
741-LSP-9019	12/11/79	User's Guide to Bed Rest Statistical Analysis Program - A. W. Nordheim
741-LSP-9020	12/17/79	Preliminary Study Requirements of Computerized Data Base and an Automatic Analysis of Human Clinical Data - A. W. Nordheim

<u>TIR No.</u>	<u>Date</u>	<u>Title and Author</u>
741-LSP-9021	12/19/79	Dynamics of Body Composition Changes During Space Flight - J. I. Leonard
741-LSP-9022	12/20/79	Requirements for an Automated System to Monitor Crew Health During Space Flight - D. Lipson
741-LSP-9023	12/26/79	A Teaching Model for the Erythropoiesis System - A. W. Nordheim and W. Chop
741-LSP-9024	12/28/79	The Parathyroid Hormone Subsystem Model - S. N. Brand